AMENDMENTS TO THE CLAIMS:

Without prejudice or disclaimer, this listing of claims will replace all prior versions and listings of claims in the application:

Claims 1-19. (Cancelled)

20. (Amended) A method for treating severe heart failure of New York Heart Association Class IV, comprising administering to a patient in need thereof a therapeutically effective amount of an active compound, 5-hydroxy-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine or a pharmaceutically acceptable salt thereof in a daily dose of less than 0.6 mg/kg.

21. (Cancelled).

22. (Amended) The method according to claim ~~21~~20, wherein the daily dose is in the range from 0.1 mg/kg to less than 0.6 mg/kg.

23. (Amended) ~~The method according to claim 20, comprising administering to the patient the active compound~~ A method for treating severe heart failure of New York Heart Association Class IV, comprising administering to a patient in need thereof a therapeutically effective amount of an active compound, 5-hydroxy-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine or a pharmaceutically acceptable salt thereof in a daily dose of 15 to 45 mg.

24. (Amended) The method according to claim ~~20~~23, comprising administering to the patient the active compound in a daily dosage of 30 mg.

REMARKS

Applicants note with appreciation the Examiner's withdrawal of prior rejections under 35 U.S.C. §§ 101, § 112, second paragraph; 102(b); and 103 over the three-reference combination of Ogawa, Gheorghiade, and Sorbera. (Office Action, pg. 2.) The presently proposed amendments to the claims and sole remaining ground for rejection are addressed below.

I. Status of the Claims

By this proposed amendment, claim 20 has been amended to incorporate the subject matter of claim 21, which has been cancelled; the dependency of claim 22 has been amended without narrowing its scope; claim 23 has been amended into independent form without narrowing its scope; and the dependency of claim 24 has been amended without narrowing its scope.

Hence, claims 20, 22, 23 and 24 are now pending pursuant to the proposed amendment.

No new matter has been added.

II. Rejection Under 35 U.S.C. § 103(a)

Claims 20-24 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ogawa (U.S. Patent No. 5,753,677) in view of Gheorghiade ("Chronic effects of vasopressin receptor blockade with tolvaptan in congestive heart failure: A randomized double-blind trial," Abstract). (Office Action, pg. 2-3.) Applicants respectfully traverse.

As stated in the Office Action, the rejection is premised on the contention that "ordinary" CHF treatments such as diuretics, used with less severe Class II-III CHF,

would have been considered suitable for use in the most severe, NYHA Class IV, CHF patients. (Office Action, pg. 3.) In particular, the Office contends that

> it is not seen unobvious from the art relied on to have employed the presently claimed compound, known to be effective as a diuretic in CHF patients, for the treatment of CHF-associated edema in any of the NYHA classes, including class IV as presently claimed.

(Office Action, pg. 3.) In essence, the Office contends that therapy for one CHF class is equally suitable therapy for another CHF class. Based on this premise, the Office evidently concludes that it would have been obvious to treat severe NYHA Class IV CHF by administering tolvaptan. (Office Action, pg. 2.)

The premise that therapies for different Class II-III CHF classes are interchangeable, however, is not supported by the evidence. To the contrary, as discussed further below, Applicants respectfully submit that the evidence shows that one skilled in the art would not necessarily use a compound suitable for the treatment of ordinary CHF (NYHA Classes I-III) as a medicament for treating severe CHF (NYHA Class IV). Indeed, there are numerous examples in the art showing that compounds effective for the treatment of NYHA Classes I-III may not be suitable for the treatment of NYHA Class IV. Likewise, agents suitable for class IV CHF may not be suitable for less severe CHF. Accordingly, as the premise is flawed and contrary to the evidence, the rejection based thereon is improper.

HEART FAILURE SOCIETY OF AMERICA GUIDELINES

The Heart Failure Society of America Guidelines, J. Card. Fail. 1999; 5: 357-82 ("Guidelines," Exhibit A) provides guidance, based upon the input and consensus of the Heart Failure Society of America as a whole, for physicians and other

health care professionals regarding the treatment of heart failure. (Guidelines, page 358.) The Guidelines indicate that β-blocker therapy should be routinely administered to clinically stable patients with mild to moderate heart failure symptom (*i.e.*, NYHA class II-III) who are on standard therapy. (Guidelines, Recommendation I, page 361.) However, the Guidelines caution that "[i]nitiation of β-blocker therapy has the potential to worsen hear failure signs and symptoms. This risk increases with the underlying severity of the hear failure that is present." (Guidelines, page 364.)

Moreover, the guideline provide as a specific recommendation that

> **[t]here is insufficient evidence to recommend the use of β-blocker therapy for inpatients or outpatients with symptoms of heart failure at rest (ie, NYHA class IV)....**

(Guidelines, Recommendation 4, page 364 (emphasis in original).) The Guidelines further instructs that "β-Blocker therapy cannot be routinely recommended for NYHA class IV patients because there are currently no clinical trial data to indicate favorable long-term efficacy and safety of β-blocker therapy." (Pg. 364 (emphasis added).) Indeed, the Guidelines specifically advise that "[a] substantial body of observational data indicates that successful institution of β-blocker therapy in patients with this degree of heart failure is problematic." (*Id.* (emphasis added).) In fact, "these agents may precipitate deterioration...." (*Id.*) Based on available clinical trial data, "the striking benefit of β-blockers in mild-to-moderate hear failure may not be extrapolated to those with severe symptoms." (*Id.*)

Thus, contrary to the premise of the present rejection that therapies used with Class II-III CHF are also suitable for treatment in class IV CHF, the Guidelines are clear that not all β-blockers suitable for the treatment of NYHA class II-III are suitable for the treatment of NYHA class IV from the viewpoint of efficacy and safety thereof.